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Supreme Court, U.S.
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No. 03-1237

IN THE

# Supreme Court of the United States

MERCK KGAA,

*Petitioner*,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE and TELIOS PHARMACEUTICALS, INC.,

*Respondents.*

**On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit**

## REPLY BRIEF

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## INTRODUCTION

This petition raises a fundamental question of statutory interpretation: What did Congress mean when it created a safe harbor from patent infringement for "uses reasonably related to the development and submission of information under a Federal law" administered by the FDA. Did it mean to exempt, as Merck contends, any use that is directed to developing data for any submission to the FDA? Or, did it mean to exempt, as the Federal Circuit held, only uses that are directed to developing "information the FDA considers in approving a drug"? Thus, the petition raises a legal question, not a factual dispute as Integra argues.

By holding that the § 271(e)(1) safe harbor exempts only information the FDA considers in approving a drug, the Federal Circuit decision will have a profound impact on pioneer drug research in this country. New pioneer drugs are approved by the FDA on the basis of information derived from human clinical trials. However, the FDA first requires information derived from pre-clinical laboratory and animal tests so that it can determine whether the drug candidate is promising enough to be tested in humans. By denying the § 271(e)(1) exemption to pre-clinical tests, the Federal Circuit has empowered patent owners to block pioneer drug research in this country before it reaches clinical testing and the safe harbor of § 271(e)(1).

The facts of this case exemplify why the Federal Circuit's decision is so important. Merck's promising cancer drug is currently undergoing clinical trials. Integra filed this case, however, before Merck began those trials and sought to enjoin Merck and Scripps from conducting the pre-clinical research needed to obtain FDA approval to initiate those trials. Had the Federal Circuit's holdings issued before this suit was filed, Integra could have preempted the clinical

trials, forced Merck to wait many years before initiating pre-clinical research, and delayed the drug's approval in this country by as many years. Many cancer victims, however, do not have those years to wait.

Integra obscures the impact of the Federal Circuit's decision by suggesting the accused experiments were "basic research aimed to identify new drug candidates." In fact, as the majority recognized, these experiments were conducted pursuant to Merck's agreement with Scripps "to fund the 'necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials' with EMD 66203 or a derivative thereof." App. 5a. That is why the question presented for review in the petition is limited to whether the 271(e)(1) safe harbor covers "animal studies of the sort that are essential to the development of new drugs, where the research will be presented to the FDA." Such studies are well down the long road of pioneer drug research, and barring them will stop drug development in this country in its tracks.

Like the Federal Circuit, Integra argues that the purpose of § 271(e)(1) was to create a safe harbor for the limited testing required for FDA approval of generic drugs. But Integra also relies on a statement by the Federal Circuit, added to the opinion in an "errata," that the safe harbor "is not limited to generic drug approval." That argument misses Merck's point – that the practical effect of the Federal Circuit's decision will be to deny the safe harbor to development of new pioneer drugs and to limit the safe harbor to generic drugs. Moreover, Integra does not explain why new pioneer drugs – which promise new cures and better treatments, require greater incentives to offset their riskier and more costly research, and would be subject to longer delays after patents expire (due to more extensive



testing) before they could be approved – are not even more deserving of the safe harbor than generic drugs.

Finally, Integra argues that this case is simply about money. Doctors and patients waiting for new cancer drugs would not agree. Throughout this case, Integra has sought injunctions – first to enjoin Scripps's research and later to enjoin Merck's future sale of any drug approved by the FDA. App. 42a-44a. Nor is this case about paying tribute to owners of biomedical "tool" patents. The Integra patents are directed to failed therapeutic drugs, not tools for biomedical research. And but for its own failure, Integra probably would have acted like most successful drug developers – choosing to use its patents to exclude competition and declining to license its patents for virtually any amount of money.

## REPLY TO INTEGRA'S OPPOSITION

Integra has neither refuted the importance of the Federal Circuit's decision nor reconciled it with this Court's decision in *Eli Lilly & Co. v. Medtronic Inc.*, 496 U.S. 661 (1990).

### I. The Question Presented Is an Issue of Law

The question that Merck has petitioned the Court to review – whether § 271(e)(1) exempts pre-clinical animal tests conducted to develop data for submission to the FDA – is an issue of law. This is analogous to the question presented in *Eli Lilly v. Medtronic* – whether § 271(e)(1) exempts tests on medical devices conducted to develop data for submission to the FDA – which this Court treated as an issue of law. The answers to both questions turn on statutory interpretation as to the scope of submissions that qualify for the § 271(e)(1) exemption.

As in *Eli Lilly*, the statutory interpretation issue presented in the petition reduces to "what submissions of information" are encompassed by the phrase "uses reasonably related to the development and submission of information under a Federal law." In *Eli Lilly*, the Federal Circuit held that § 271(e)(1) only exempted uses related to submissions for generic drugs, but this Court held that the statute exempted *any submission to the FDA*, including those related to medical devices. Here, the Federal Circuit held that § 271(e)(1) only exempts uses related to clinical submissions for drug approval, and the petition asks this Court whether it meant what it said in *Eli Lilly* in holding that the statute exempts uses related to any submission to the FDA, including pre-clinical submissions. In both cases, the question is an issue of law.

Consistent with this analysis, the Federal Circuit affirmed the district court judgment by engaging in statutory interpretation and making a ruling of law. The Federal Circuit's analysis focused on the statutory language and the legislative history. App. 8a-14a. Then the Federal Circuit affirmed the district court judgment by ruling "this court discerns no error in the district court's interpretation of 35 U.S.C. § 271(e)(1)." App. 14a.

## II. The Federal Circuit Decision Conflicts With the Language of the Statute, Its Legislative History, and This Court's Precedent

### A. The Federal Circuit Decision Effectively Limits Section 271(e)(1) to Testing of Generic Drugs

Integra misses the point when it argues that the Federal Circuit stated "the scope of the safe harbor is not limited to generic drug approval." Merck never suggested otherwise. Merck argued in its petition that, by excluding pre-clinical



research from the § 271(e)(1) exemption, the Federal Circuit empowered patent owners to preempt the clinical testing of new pioneer drugs that is protected by the exemption, and effectively limited the safe harbor to testing of generic drugs.

The Federal Circuit limited the safe harbor for new pioneer drugs by holding that "the district court correctly confined the § 271(e)(1) exemption to activity that 'would contribute (relatively directly)' to information the FDA considers *in approving a drug*." App. 13a (emphasis added). The Federal Circuit rejected "an interpretation of § 271(e)(1) that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a patented pioneer drug already on the market," i.e., a generic drug. App. 13a. As a consequence, the Federal Circuit ruled that the safe harbor does not encompass "pre-clinical research" conducted to "identif[y] the best drug candidate to subject to future clinical testing under the FDA processes." App. 10a.

Other courts have recognized and acknowledged the practical effect of limiting the § 271(e)(1) exemption to clinical research. As one court explained, if that were the case, "the exemption would never be reached because the underlying preliminary research and development work could not be undertaken [in the first instance]." *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833, 2001 WL 1512597 at *6 (S.D.N.Y. Nov. 28, 2001). Another court concluded that excluding the research needed to create new pioneer drugs from the safe harbor "would chill parties from engaging in the very pre-approval testing that Congress sought to encourage." *See Nexell Therapeutics, Inc. v. AmCell Corp.*, 199 F. Supp. 2d 197, 204 (D. Del. 2002). And summarizing the law before the Federal Circuit decision, the *Nexell* court observed: "courts have determined that activities should only be found to

exceed the scope of the § 271(e)(1) exemption when they have no objectively reasonable application towards obtaining FDA approval." *Id.* at 204-05.

### B. Section 271(e)(1) Exempts Activities Reasonably Related to the Development and Submission of Information Under the FDA's "Entire Statutory Scheme of Regulation"

Integra repeats the error made by the Federal Circuit and mischaracterizes the § 271(e)(1) exemption as limited to activities reasonably related to "FDA approval." The statutory language is not so limited. The statute exempts activities reasonably related to "the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products."

In *Eli Lilly v. Medtronic*, this Court held that the safe harbor of § 271(e)(1) exempts the development and submission of information under the FDA's "entire statutory scheme of regulation." 496 U.S. at 666-67. Thus, use of a patented invention to develop and submit information under any section of the Food Drug and Cosmetic Act (FDCA) – not just the limited testing required for approval of generic drugs or the clinical testing required for approval of new pioneer drugs – is exempt from infringement. The Federal Circuit, however, never analyzed the FDCA to determine what information the FDA requires or considers during the regulatory review process for new pioneer drugs.

In fact, the FDCA requires submission of both clinical and preclinical testing. Before the FDA will permit human clinical trials of a pioneer new drug to begin, 21 U.S.C. § 355(i)(1)-(3) of the FDCA requires submission of "preclinical tests (including tests on animals) of such drug



adequate to justify the proposed clinical testing." Clinical testing will not be approved if the FDA finds that "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." 21 U.S.C. § 355(i)(3).

One of the pre-clinical submissions required by the FDA is an Investigatory New Drug Application (IND), which includes the following information:

1. the rationale for the study, which is based on accumulated data of safety and potential therapeutic efficacy;

2. the physical, chemical, and biological characteristics of the drug, as well as pharmacological, toxicological, and efficacy data sufficient for an investigator conducting the clinical trials to decide whether to give the drug to his patients;

3. an introduction that gives the background of the drug and discloses everything known about the drug up to that point; and

4. comparative data supporting any change in the choice of the drug candidate during the preclinical studies.

21 C.F.R. § 312.23, A7404-06, A7408, A7400-01.

The tests accused of infringement in this case were performed to obtain regulatory approval of an IND, A7167-68, A7176-93, A6988-99, A7500-01, A6650-55, A10215-352, A10878-953, and fall squarely within the pre-clinical testing required by the FDCA. For example, in one set of accused experiments, Scripps administered compound EMD 121974 to nude mice with tumors to demonstrate safety,

pharmacology, and efficacy of the compound in an IND. A11063, A7191. If these tests are deemed "far beyond" the safe harbor, then it is clear that under the Federal Circuit's interpretation of 271(e)(1), virtually all pre-clinical testing will fall outside the safe harbor. Consequently, the 271(e)(1) exemption will never be reached in new pioneer drug development during the term of any relevant patents, thereby effectively limiting the safe harbor to testing of generic drugs.

### C. The Legislative History Does Not Limit the Section 271(e)(1) Exemption to Tests Required for Approval of Generic Drugs

In reaching its decision, the Federal Circuit relied principally on the legislative history of § 271(e)(1), concluding that the statute was intended "to facilitate the immediate entry of safe, effective generic drugs into the marketplace upon expiration of a pioneer drug patent." App. 12a. In its opposition, Integra also relies on references to generic drugs in the legislative history to argue that § 271(e)(1) is limited to testing required for FDA approval of generic drugs.

These interpretations of the legislative history conflict with this Court's decision in *Eli Lilly* in at least two regards. First, this Court concluded in *Eli Lilly v. Medtronic* that the legislative history of this statute "sheds no clear light" on its intended scope. 496 U.S. 661, 669. And second, this Court expressly held in *Eli Lilly* that § 271(e)(1) was not limited to testing required for approval of generic drugs. *Id.* at 668-69, 679.

What is clear from the legislative history of § 271(e)(1) is that Congress sought to encourage the development of new drugs and to prevent the *de facto* patent term extension



caused by the lengthy testing required by the FDA. Those policies apply to development of pioneer drugs with at least equal force as to generic drugs. Indeed, because pioneer drugs often have unique attributes and must undergo lengthy pre-clinical and clinical testing and generics are only mimics of existing drugs and require only bioequivalence testing, pioneer drug development is even more deserving of the § 271(e)(1) exemption than generic drug development.

## III. The Federal Circuit's Decision Departs Dramatically from Current Law and Practice and Will Profoundly Impact Research and Development of New Pioneer Drugs in This Country

Since *Eli Lilly*, other courts, including other panels of the Federal Circuit, have interpreted § 271(e)(1) as exempting a broad range of research activities by parties seeking FDA approval for new drugs and medical devices. *See, e.g., Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1523 (Fed. Cir. 1992), where the Federal Circuit held that displays of medical devices at trade shows to solicit clinical investigators for clinical trials were exempt activities because "device sponsors are responsible for selecting qualified investigators and providing them with the necessary information to conduct clinical testing." Just as these demonstrations at trade shows were a reasonable predicate to conducting clinical trials of a medical device, preclinical testing is a reasonable, and indeed FDA-mandated, predicate to conducting clinical trials of a new pioneer drug.

This ruling will profoundly impact the public welfare and the biomedical research industry in this country because it will affect research for virtually every new pioneer drug. It cannot be assumed, as the Federal Circuit did, that licenses for research will be available from patent owners. More

typically, drug patents are used to exclude competition. As a consequence, the development of some new pioneer drugs will be foreclosed or delayed. In such cases, the public will be denied or delayed access to new pioneer drugs that may be safer or more effective than existing drugs, and victims of diseases like cancer will needlessly suffer and die.

## CONCLUSION

Because the Federal Circuit's decision will profoundly impact new pioneer drug research in this country and conflicts with this Court's decision in *Eli Lilly v. Medtronic* that § 271(e)(1) exempts development of information for the "entire statutory scheme or regulation" of the FDA, this Court should grant the petition for a writ of certiorari.

Respectfully submitted,

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